IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Gerard M. Jensen et al.	Art Unit	: 1612
Serial No.	: 10/723,423	Confirm No.	: 6232
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		Docket	: 01992.005US1
Title	: LIPOSOMAL FORMULATIONS		

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Final Office Action for this application was mailed June 24, 2009, and a Notice of Appeal was submitted December 23, 2009. Applicant respectfully appeals to the Board for review of the Examiner's final rejection.

(1) Real Party in Interest.

The real party in interest is Gilead Sciences, Inc. The right of Gilead Sciences, Inc. to take action in the subject application was established by assignment from the inventors to Gilead Sciences, Inc. as recorded at Reel 016496, Frame 0930.

(2) Related Appeals and Interferences.

There are no related appeals or interferences.

(3) Status of Claims.

The final Office Action mailed June 24, 2009 rejected claims 24-30 and 39-63. No claims have been allowed. Claims 1-53 and 59-63 have been canceled. Therefore, Applicant respectfully appeals the final rejection of claims 54-58.

(4) Status of Amendments.

Claims 29 and 30 were amended on December 23, 2009, subsequent to the Final Office Action mailed June 24, 2009 to depend from pending claims 54-58.

An Advisory Action was mailed on January 15, 2010, which indicated that the amendments to the claims of December 23, 2009 would not be entered.

Filed concurrently herewith, Applicant submits an Amendment After Appeal to cancel claims 1-53 and 59-63. The appealed claims are claims 54-58.

(5) Summary of the Claimed Subject Matter.

The claimed subject matter provides formulations comprising a lipophobic therapeutic agent encapsulated in a liposome.

Independent claim 54 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1. Independent claim 54 finds support in the application as filed in original claims 1 and 24, at page 11 at lines 1-3 (paragraph [0062]), in the Table at page 15, and in the Table in Example 1 at page 21.

Independent claim 55 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol in a ratio of about 2:1. Independent claim 55 finds support in the application as filed in original claims 1 and 25, at page 11 at lines 4-6 (paragraph [0063]), in the Table at page 15, and in the Table in Example 1 at page 21.

Independent claim 56 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1. Independent claim 56 finds support in the application as filed in original claims 1 and 26, at page 11 at lines 7-9 (paragraph [0064]), in the Table at page 15, and in the Table in Example 1 at page 21.

Independent claim 57 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1. Independent claim 57 finds support in the application as filed in original claims 1 and 27, at page 11 at lines 10-12 (paragraph [0065]), in the Table at page 15, and in the Table in Example 1 at page 21.

Independent claim 58 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1. Independent claim 58 finds support in the application as filed in original claims 1 and 28, at page 11 at lines 13-15 (paragraph [0066]), in the Table at page 15, and in the Table in Example 1 at page 21.

(6) Grounds of Rejection to be Reviewed on Appeal.

The issues being appealed are the following:

(A) Whether claims 54-58 fail to comply with 35 U.S.C.§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; and

(B) Whether claims 54-58 are unpatentable under 35 U.S.C. § 103(a) over the following:

(1) Hersch (US Patent No. 5,759,571, hereinafter "Hersch")) by itself or in combination with Allen (*Biochimica et Biophysica Acta*, 597(1980): 418-426, hereinafter "Allen"), Fujii (US Patent No. 5,328,678, hereinafter "Fujii"), O'Rear (US Patent No. 5,503,850, hereinafter "O'Rear") individually or in combination;

(2) Lopez-Berestein (US Patent No. 5,032,404, hereinafter "Lopez-Berestein") by itself or in combination with Allen, Fujii, and O'Rear, individually or in combination, further in view of Hersch.

(3) Hays (US Patent No. 5,869,092, hereinafter "Hays") by itself or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination; and

(4) Hays alone or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination as set forth above, further in view of Anaissie (US Patent No. 4,999,199, hereinafter "Anaissie").

(7) Arguments

The science of liposomes, including liposomal delivery of therapeutic agents, has been extensively studied. Liposomes can be made from a wide variety of components and the relative amounts of these components can vary widely from system to system. Additionally, the inclusion of therapeutic agents, with inherently different physical properties (*e.g.*, lipophobic agents), within liposomes introduces another source of variability. Thus, the possible number of discreet liposome systems is extremely large.

Certain specific long-circulating liposomes have been studied in human clinical trials. Specification at page 2, lines 9-16. A significant problem with such long-circulating liposomes, however, results from an inability to properly balance the enhanced circulation lifetime of the liposomes with specific drug release profiles. Although investigators have successfully increased the circulation lifetimes of drugs encapsulated in pegylated liposomes, which beneficially promotes accumulation of the liposomes at tumor growth sites, they have been unable to realize acceptable drug release profiles from these liposomes for certain therapeutic agents. Specification at page 2, lines 23-29.

Notwithstanding the significant body of academic and commercial research that has been devoted to liposomal drug delivery and the large body of existing literature that describes this research, at the time of Applicant's discovery there remained a need for liposomal formulations that could be used to deliver non-amphiphilic therapeutic agents at therapeutically useful release rates. Specification at page 3, lines 17-19. Applicant developed such systems, *i.e.*, liposomal systems that provide intermediate elimination half-lives for lipophobic therapeutic agents. Thus, the liposome systems recited in the instant claims can improve the therapeutic index and the activity of the lipophobic agents. Additionally, the drug release profiles for the liposome systems recited in the instant claims are an improvement over the insufficient drug release profiles of the previously available long-circulating liposomes. Thus, the liposome systems recited in the instant claims solve the problem of inadequate drug release encountered in earlier long circulating liposomes. Specification at page 2, lines 28-29. No prior liposome systems provided this combination of useful properties for delivering lipophobic therapeutic agents.

A. Claims 54-58 comply with 35 U.S.C. § 112, second paragraph and are not indefinite.

The second paragraph of 35 U.S.C. § 112 states the following:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Page 2-3 of the Final Office Action mailed June 24, 2009 states that the independent claims 54-58 recite "two functional limitations 1 and 2, which contradict each other in terms of half-life." Applicant respectfully asserts that none of the pending claims 54-58 recite language regarding half-life of the therapeutic agent. Accordingly, the Examiner erred in rejecting claims 54-58 under 35 U.S.C. § 112, second paragraph. Reversal of the Examiner's rejection of claims 54-58 is appropriate and is respectfully requested.

B. Claims 54-58 are patentable over the cited references under 35 U.S.C. § 103(a)

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the framework for the objective analysis of determining obviousness under 35 U.S.C. § 103(a) is stated in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The factual analysis involves (1) determining the scope and content of the prior art, (2) ascertaining the differences between the prior art and the claims at issue, and (3) resolving the level of ordinary skill in the pertinent art. Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, often called "secondary considerations," include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. Cited documents must be considered in their entirety, and it is not permissible to pick and choose from any one document only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such document fairly suggests to one of ordinary skill in the art (*see, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986) and *In re Wesslau*, 353 F.2d 238, U.S.P.Q. 391 (C.C.P.A. 1965)).

Applicant respectfully submits that the Examiner has not demonstrated that any of claims 54-58 are *prima facie* obvious in view of the cited documents, for example, because the Examiner has not established that the cited documents teach or suggest the claim limitations of

each separate claim. And, even if, for the sake of argument, the cited documents teach or suggests all the claim limitations, Applicant respectfully submits that the Examiner has not established the suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention of each separate claim. Because of the specific elements of each claim, each claim is argued separately.

(1) Rejection of claims 54-58 under 35 U.S.C. § 103(a) as being unpatentable over Hersch (US Patent No. 5,759,571, hereinafter "Hersch")) by itself or in combination with Allen (*Biochimica et Biophysica Acta*, 597(1980): 418-426, hereinafter "Allen"), Fujii (US Patent No. 5,328,678, hereinafter "Fujii"), O'Rear (US Patent No. 5,503,850, hereinafter "O'Rear") individually or in combination

Claim 54

Claim 54 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises hydrogenated soybean phosphatidyl choline:Cholesterol:Distearoyl Phosphatidyglycerol (HSPC:Cholesterol:DSPG) in a ratio of about 4:1:0.1. Hersch at col. 6, lines 11-17 recites liposomes with a preferred ratio of HSPC:cholesterol:DSPG of about 2:1:0.1 and that "[o]ther preferred formulations include DSPG in a molar amount of 0 to 20% and most preferably in a molar amount of less than 5%." The Office Action has provided no text reference or knowledge why the 2:1:0.1 HSPC:cholesterol:DSPG ratio mentioned by Hersch teaches the ratio of 4:1:0.1 (*i.e.*, where the amount of HSPC is double of that taught by Hersch) as recited in claim 54. Even if Hersch discusses that the amount of DSPG may vary, there is no teaching or suggestion that the amount of HSPC:cholesterol is 4:1. It is the change in ratio that achieves the desired properties of the liposomes described in Claim 54, and a 2:1:0.1 HSPC:Cholesterol:DSPG liposome has very long half life and very slow drug release. Thus, Hersch does not teach all of the features of claim 54.

Further, the Hersch formula of 2:1:0.1 HSPC:Chol:DSPG would have a very long half life as compared to the presently claimed ratio that has an intermediate release value, which imparts an unexpected result to the present claims as compared to what is taught by Hersch. As discussed above, the Applicant's system provided a needed balance between elimination half-life times that

were too short or were too long. Applicant's system provides intermediate elimination half-lives for lipophobic therapeutic agents. The drug release profiles for the liposome systems recited in the instant claims are an improvement over the insufficient drug release profiles of the previously studied long-circulating liposomes. Thus, the liposome systems recited in the instant claims solve the problem of inadequate drug release of previously-known liposomes like those discussed in Hersch.

As characterized by the Examiner, the Allen, Fujii and O'Rear references discuss liposomes that include cholesterol. However, these citations do not speak to the difference between the ratios of phosphatidylglycerol lipids to phosphatidylcholine lipids as discussed above and thus do not remedy the deficiencies of Hersch. These references all utilize different liposomal constituents and result in significantly different liposomes. The liposomes of Allen are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54. Instead, Allen used egg phosphatidylcholine (egg lecithin), dipalmitoylphosphatidylcholine (DPPC) or distearoylphosphatidylcholine (DSPC), none of which are recited by the present claims. Allen at page 420. The liposomes of Allen are significantly less stable than the liposomes described in the instant invention, causing Allen's liposomes to leak due to osmotic stress while the presently claimed liposomes do not. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Allen.

The liposomes of O'Rear are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54. Instead, O'Rear used 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC), which is not recited by the present claims. O'Rear at col. 5, line 51. As discussed at the paragraph bridging pages 11-12 of the March 9, 2009 Response to the Office Action mailed September 9, 2008, the liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of the liposome. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by O'Rear.

Lastly, the liposomes of Fujii are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54. Instead, Fujii used distearoylphosphatidylcholine (DSPC) and cholesterol, which is not recited by the present claims. Fujii at col. 3, lines 1-12 and 46-48 and col. 4, lines 31-32. The liposomes of Fujii are highly stable and thus are slow release liposomes, whereas the liposomes of

the instant invention are intermediate release liposomes. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Fujii.

Applicant requests that the Board reverse the Examiner's rejection of claim 54 as being obvious over Hersch, Allen, O'Rear and Fujii.

Claim 55

Claim 55 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dielaidoyl phosphatidyl choline:Cholesterol (DEPC:Cholesterol) in a ratio of about 2:1. Hersch does not teach or suggest a formulation of DEPC:Cholesterol. Thus, Hersch does not teach all of the features of claim 55, because it does not teach the elements or ratios recited in claim 55.

As characterized by the Examiner, Allen discusses liposomes that include cholesterol. However, as discussed above, the liposomes of Allen are not formulated from DEPC:Cholesterol as recited in claim 55. The liposomes of Allen are significantly less stable than the liposomes described in the instant invention, causing Allen's liposomes to leak due to osmotic stress while the presently claimed liposomes do not. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Allen.

The liposomes of O'Rear are not formulated from DEPC:Cholesterol as recited in claim 55. Instead, O'Rear used 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC), which is not recited by the present claims. O'Rear at col. 5, line 51. The liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of the liposome. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by O'Rear.

The liposomes of Fujii are not formulated from DEPC:Cholesterol as recited in claim 55. Instead, as discussed above, Fujii used distearoylphosphatidylcholine (DSPC) and cholesterol, which is not recited by the present claims. The liposomes of Fujii are highly stable and thus are slow release liposomes, whereas the liposomes of the instant invention are intermediate release liposomes. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Fujii.

The primary reference does not teach DEPC:Cholesterol as recited in claim 55; this defect is not corrected by any of the secondary documents. Therefore, even if the cited documents were combined as suggested by the Examiner, the combination would not include all the elements of the claimed invention. Therefore, the claim is not *prima facie* obvious over the cited documents.

Applicant requests that the Board reverse the Examiner's rejection of claim 55 as being obvious over Hersch, Allen, O'Rear and Fujii.

Claim 56

Claim 56 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dielaidoyl phosphatidyl choline:Cholesterol:Distearoyl Phosphatidyglycerol (DEPC:Cholesterol:DSPG) in a ratio of about 2:1:0.1. Hersch does not teach or suggest a formulation of DEPC:Cholesterol:DSPG. Thus, Hersch does not teach all of the features of claim 56.

Allen discusses liposomes that include cholesterol, but does not speak to the difference between the ratios of phosphatidylglycerol lipids to phosphatidylcholine lipids as discussed above and thus do not remedy the deficiencies of Hersch. As discussed above, the liposomes of Allen are not formulated from DEPC:Cholesterol:DSPG as recited in claim 56, but instead egg lecithin, DPPC or DSPC. The liposomes of Allen are significantly less stable than the liposomes described in the instant invention, causing Allen's liposomes to leak due to osmotic stress while the presently claimed liposomes do not. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Allen.

The liposomes of O'Rear are not formulated from DEPC:Cholesterol:DSPG as recited in claim 56. Instead, as discussed above, O'Rear used POPC, which is not recited by the present claims. The liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of the liposome. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by O'Rear.

The liposomes of Fujii are not formulated from DEPC:Cholesterol:DSPG as recited in claim 56. Instead, as discussed above, Fujii used DSPC and cholesterol, which is not recited by the present claims. The liposomes of Fujii are highly stable and thus are slow release liposomes,

whereas the liposomes of the instant invention are intermediate release liposomes. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Fujii.

The primary reference does not teach DEPC:Cholesterol:DSPG as recited in claim 56; this defect is not corrected by any of the secondary documents. Therefore, even if the cited documents were combined as suggested by the Examiner, the combination would not include all the elements of the claimed invention. Therefore, the claim is not *prima facie* obvious over the cited documents.

Applicant requests that the Board reverse the Examiner's rejection of claim 56 as being obvious over Hersch, Allen, O'Rear and Fujii.

Claim 57

Claim 57 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dioleoyl phosphatidyl choline:Cholesterol (DOPC:Cholesterol) in a ratio of about 2:1. Hersch does not teach or suggest a formulation comprising DOPC:Cholesterol in any ratio. Thus, Hersch does not teach all of the features of claim 57.

As characterized by the Examiner, Allen discusses liposomes that include cholesterol. The liposomes of Allen, however, are not formulated from DOPC:Cholesterol as recited in claim 57. The liposomes of Allen are significantly less stable than the liposomes described in the instant invention, causing Allen's liposomes to leak due to osmotic stress while the presently claimed liposomes do not. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Allen.

The liposomes of O'Rear are not formulated DOPC:Cholesterol as recited in claim 57. The liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of the liposome. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by O'Rear.

The liposomes of Fujii are not formulated from DOPC:Cholesterol as recited in claim 57. Instead, Fujii used distearoylphosphatidylcholine (DSPC) and cholesterol, which is not recited by

the present claims. The liposomes of Fujii are highly stable and thus are slow release liposomes, whereas the liposomes of the instant invention are intermediate release liposomes. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Fujii.

The primary reference does not teach DOPC:Cholesterol as recited in claim 57; this defect is not corrected by any of the secondary documents. Therefore, even if the cited documents were combined as suggested by the Examiner, the combination would not include all the elements of the claimed invention. Therefore, the claim is not *prima facie* obvious over the cited documents.

Applicant requests that the Board reverse the Examiner's rejection of claim 57 as being obvious over Hersch, Allen, O'Rear and Fujii.

Claim 58

Claim 58 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dimyristoyl phosphatidyl choline:Cholesterol:Distearoyl Phosphatidyglycerol (DMPC:Cholesterol:DSPG) in a ratio of about 2:1:0.1. Hersch does not teach or suggest a formulation of DMPC:Cholesterol in a ratio of about 2:1:0.1. Thus, Hersch does not teach all of the features of claim 58.

As characterized by the Examiner, the Allen, Fujii and O'Rear references discuss liposomes that include cholesterol. Allen utilizes different liposomal constituents that provide significantly different liposomes. The liposomes of Allen are not formulated from DMPC:Cholesterol:DSPG as recited in claim 58. The liposomes of Allen are significantly less stable than the liposomes described in the instant invention, causing Allen's liposomes to leak due to osmotic stress while the presently claimed liposomes do not. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Allen.

The liposomes of O'Rear are not formulated from DMPC:Cholesterol:DSPG as recited in claim 58. Instead, O'Rear used 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC), which is not recited by the present claims. The liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of

the liposome. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by O'Rear.

Lastly, the liposomes of Fujii are not formulated from DMPC:Cholesterol:DSPG as recited in claim 58. Instead, Fujii used distearoylphosphatidylcholine (DSPC) and cholesterol, which is not recited by the present claims. The liposomes of Fujii are highly stable and thus are slow release liposomes, whereas the liposomes of the instant invention are intermediate release liposomes. Thus, in addition to the present liposomes being different structurally, they are also functionally distinguishable over those discussed by Fujii.

The primary reference does not teach DMPC:Cholesterol:DSPG as recited in claim 58; this defect is not corrected by any of the secondary documents. Therefore, even if the cited documents were combined as suggested by the Examiner, the combination would not include all the elements of the claimed invention. Therefore, the claim is not *prima facie* obvious over the cited documents.

Applicant requests that the Board reverse the Examiner's rejection of claim 58 as being obvious over Hersch, Allen, O'Rear and Fujii.

(2) Rejection of claims 54-58 under 35 U.S.C. § 103(a) as being unpatentable over Lopez-Berestein (US Patent No. 5,032,404, hereinafter "Lopez-Berestein") by itself or in combination with Allen, Fujii, and O'Rear, individually or in combination, further in view of Hersch

Claim 54

Claim 54 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1.

Lopez-Berestein describes a system wherein a hydrophobic therapeutic agent is trapped in the lipid bilayer of the liposome, rather than being located in the hydrophilic interior of the liposome. In contrast, the instant claims recite a lipophobic (*i.e.*, a hydrophilic) therapeutic agent. The specification at page 8 recites:

> The term "lipophobic therapeutic agent" includes compounds that are water soluble enough to achieve a useful level of loading by passive encapsulation and that are significantly impermeable once loaded. The term excludes agents that are both amphiphilic and that can be effectively gradient loaded into liposomes.

Accordingly, the formulations of the invention are typically prepared by passive loading of liposomes.

Further, Lopez-Berestein teaches away from the recitations of the rejected claims. The liposomes of Lopez-Berestein are not formulated from HSPC:Cholesterol:DSPG as recited in claim 54. In contrast, Lopez-Berestein discusses "DMPG" while failing to discuss "DSPG." Moreover, Lopez-Berestein at column 8, lines 4-7 discusses liposomes comprising dimyristoyl phosphatdylglcerol (DMPG) and dimyristol phosphatidylcholine (DMPC) in ratios of about 1:10 and 10:1 and more preferably in a ratio of about 3:7. Thus, claim 54 recites different specific lipids as compared to those taught by Lopez-Berestein, and the ratio of phosphatidylglycerol lipids to phosphatidylcholine lipids in all of the claims 54-58 is significantly different even when comparing the most similar ratios (40:1 versus 10:1). The Examiner has not provided any scientific reasoning why one would be led to a ratio of 40:1 from the Lopez-Berestein ratio of 10:1. Accordingly, claim 54 would not be obvious when the art teaches a ratio of about 10:1.

Hersch, Allen, Fujii, and O'Rear neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present claimed invention. As discussed above, Hersch used HSPC:cholesterol:DSPG, but at a significantly different ratio. Allen used egg phosphatidylcholine (egg lecithin), DPPC or DSPC, none of which are recited by the present claims. Fujii used DSPC and cholesterol, which combination is not recited by the present claims. O'Rear used 1-palmitoyl-2-oleo phosphatidyl choline (POPC), which is not recited by the present claims.

Accordingly, since the Lopez-Berestein, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the formulation or ratio of phospholipids and cholesterol to form the liposomes recited in claim 54, Applicant requests that the Board reverse the Examiner's rejection of claims 54 as being obvious over Lopez-Berestein, Hersch, Allen, Fujii and O'Rear.

Claim 55

Claim 55 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol in a ratio of about 2:1.

The liposomes of Lopez-Berestein are not formulated from DEPC:Cholesterol in a ratio of about 2:1 as recited in claim 55. Lopez-Berestein at col. 15, lines 13-25 and Table 5 mention DEPC:Cholesterol, but at a significantly different ratio (9:1) as opposed to the claimed ratio of 2:1. Thus, claim 55 recites a different specific ratio of DEPC:Cholesterol as compared to what is taught by Lopez-Berestein. The Examiner has not provided any scientific reasoning why one would be led to the claimed ratio.

Hersch, Allen, Fujii, and O'Rear neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present claimed invention. As discussed above, Hersch does not teach or suggest a formulation of DEPC:Cholesterol. Allen used egg lecithin, DPPC or DSPC, none of which are recited by the present claims. Fujii used DSPC and cholesterol, which is not recited by the present claims. O'Rear used POPC, which is not recited by the present claims. Accordingly, since the Lopez-Berestein, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the formulation or ratio of phospholipids and cholesterol to form the liposomes recited in claim 55, Applicant requests that the Board reverse the Examiner's rejection of claims 55 as being obvious over Lopez-Berestein, Hersch, Allen, Fujii and O'Rear.

Claim 56

Claim 56 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1.

The liposomes of Lopez-Berestein are not formulated from DEPC:Cholesterol:DSPG as recited in claim 56. Thus, claim 56 recites different specific lipids as compared to those taught by Lopez-Berestein, and the ratio of phosphatidylglycerol lipids to phosphatidylcholine lipids in all of the pending claims is significantly different from what is taught by Lopez-Berestein.

Hersch, Allen, Fujii, and O'Rear neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present claimed invention. As discussed above, Hersch does not teach or suggest a formulation of

DEPC:Cholesterol:DSPG. Allen used egg phosphatidylcholine (egg lecithin), DPPC or DSPC, none of which are recited by the present claims. Fujii used DSPC and cholesterol, which is not recited by the present claims. O'Rear used POPC, which is not recited by the present claims. Accordingly, since the Lopez-Berestein, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the formulation or ratio of phospholipids and cholesterol to form the liposomes recited in claim 56, Applicant requests that the Board reverse the Examiner's rejection of claims 56 as being obvious over Lopez-Berestein, Hersch, Allen, Fujii and O'Rear.

Claim 57

Claim 57 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1.

The liposomes of Lopez-Berestein are not formulated from DOPC:Cholesterol as recited in claim 57. Thus, claim 57 recites different specific lipids as compared to those taught by Lopez-Berestein. The Examiner has not provided any scientific reasoning why one would be led to the claimed ratio.

Hersch, Allen, Fujii, and O'Rear neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present claimed invention. Hersch does not teach or suggest a formulation of DOPC:Cholesterol. Allen used egg phosphatidylcholine (egg lecithin), DPPC or DSPC, none of which are recited by the present claims. Fujii used DSPC and cholesterol, which is not recited by the present claims. O'Rear used POPC, which is not recited by the present claims. Accordingly, since the Lopez-Berestein, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the formulation recited in claim 57, Applicant requests that the Board reverse the Examiner's rejection of claims 57 as being obvious over Lopez-Berestein, Hersch, Allen, Fujii and O'Rear.

Claim 58

Claim 58 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1.

The liposomes of Lopez-Berestein are not formulated from DMPC:Cholesterol:DSPG as recited in claim 58. Thus, claim 58 recites different specific lipids as compared to those taught by Lopez-Berestein, and the ratio of phosphatidylglycerol lipids to phosphatidylcholine lipids in all of the pending claims is significantly different from what is taught by Lopez-Berestein. The Examiner has not provided any scientific reasoning why one would be led to the claimed ratio.

Hersch, Allen, Fujii, and O'Rear neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present claimed invention. Hersch does not teach or suggest a formulation of DOPC:Cholesterol. Allen used egg phosphatidylcholine (egg lecithin), DPPC or DSPC, none of which are recited by the present claims. Fujii used DSPC and cholesterol, which is not recited by the present claims. O'Rear used POPC, which is not recited by the present claims. Accordingly, since the Lopez-Berestein, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the formulation recited in claim 58, Applicant requests that the Board reverse the Examiner's rejection of claims 58 as being obvious over Lopez-Berestein, Hersch, Allen, Fujii and O'Rear.

(3) Rejection of claims 55-56 and 58 under 35 U.S.C. § 103(a) as being unpatentable over Hays (US Patent No. 5,869,092, hereinafter "Hays") by itself or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination

Claim 55

Claim 55 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol in a ratio of about 2:1.

Hays describe liposome systems that are very different than the liposomes recited in the instant claims. Hays discusses the use of DPPC, egg phosphatidylethanolamine, DEPC and DMPC (col. 9, lines 35-38), and specifically made liposomes from DEPC (Example 1). Hays

states that a sterol such as cholesterol may be present, and when a sterol such as cholesterol is present, the mole ratio of sterol to phospholipid is generally from about 0.1:1.0 (col. 8, lines 4-6). This ratio differs significantly from the ratio recited in the present claims, which has a sterol:phospholipid ratio of 4:1 or 2:1. This structural difference imparts a significant functional distinction to the presently claimed invention. The liposomes described by Hays would not have intermediate release properties. Although Hays describes a liposome comprising DEPC and mentions in a broad manner that cholesterol may be present, no guidance is provided relative to the amounts of cholesterol that would lead to a liposome with intermediate release of a lipophobic agent. Although Hays mentions negatively charged phospholipids, Hays does not suggest or teach either the lipids recited in instant claims or the ratios of the lipids to one another. The proper selection of both of these elements provides for liposomes that have intermediate release properties consistent with the functional element of the claims.

The cited references Allen, Fujii and O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes such as those described in claim 55. Furthermore, Hersch does not teach or suggest the compositions or ratios of the formulations of claim 55. Therefore, there is no explicit or inherent reason to combine the cited references to arrive at the liposomes of the rejected claims.

Accordingly, the Hays, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the liposomes recited in the instant claims. Therefore, Applicant requests that the Board reverse the Examiner's rejection of claim 55 as being obvious over Hays, Hersch, Allen, Fujii and O'Rear.

Claim 56

Claim 56 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1.

Hays discusses the use of DEPC to make liposomes (Example 1). Hays states that a sterol such as cholesterol may be present in the liposomes therein, and when a sterol such as cholesterol is present, the mole ratio of sterol to phospholipid is generally from about 0.1:1.0 (col. 8, lines 4-6). As discussed above, this ratio differs significantly from the ratio recited in the claim 56, which has a sterol:phospholipid ratio of 2:1. This structural difference imparts a

significant functional distinction to the presently claimed invention. The liposomes described by Hays would not have intermediate release properties. Although Hays describes a liposome comprising DEPC and mentions in a broad manner that cholesterol may be present, no guidance is provided relative to the amounts of cholesterol that would lead to a liposome with intermediate release of a lipophobic agent. Although Hays mentions negatively charged phospholipids, Hays does not suggest or teach either the lipids recited in instant claims or the ratios of the lipids to one another. The proper selection of both of these elements provides for liposomes that have intermediate release properties consistent with the functional element of the claims.

The cited references Allen, Fujii and O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes such as those described in the rejected claims. Furthermore, Hersch does not teach or suggest the compositions or ratios of the formulation of claim 56. Therefore, there is no explicit or inherent reason to combine the cited references to arrive at the liposomes of the rejected claims.

Accordingly, the Hays, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the liposomes recited in the instant claims. Therefore, Applicant requests that the Board reverse the Examiner's rejection of claim 56 as being obvious over Hays, Hersch, Allen, Fujii and O'Rear.

Claim 58

Claim 58 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1.

Hays discusses the use of DPPC, egg phosphatidylethanolamine, DEPC and DMPC (col. 9, lines 35-38), and specifically made liposomes from DEPC (Example 1). Hays states that a sterol such as cholesterol may be present, and when a sterol such as cholesterol is present, the mole ratio of sterol to phospholipid is generally from about 0.1:1.0 (col. 8, lines 4-6). This ratio differs significantly from the ratio recited in the present claims, which has a sterol:phospholipid ratio of 2:1. This structural difference imparts a significant functional distinction to the presently claimed invention. The liposomes described by Hays would not have intermediate release properties. Although Hays describes a liposome comprising DEPC and mentions in a broad manner that cholesterol may be present, no guidance is provided

relative to the amounts of cholesterol that would lead to a liposome with intermediate release of a lipophobic agent. Although Hays mentions negatively charged phospholipids, Hays does not suggest or teach either the lipids recited in instant claims or the ratios of the lipids to one another. The proper selection of both of these elements provides for liposomes that have intermediate release properties consistent with the functional element of the claims.

The cited references Allen, Fujii and O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes such as those described in the rejected claims. Furthermore, Hersch does not teach or suggest the compositions or ratios of the formulations of claim 58. Therefore, there is no explicit or inherent reason to combine the cited references to arrive at the liposomes of the rejected claims.

Accordingly, the Hays, Hersch, Allen, Fujii and O'Rear references when taken singly or in combination do not teach or suggest the liposomes recited in the instant claims. Therefore, Applicant requests that the Board reverse the Examiner's rejection of claim 58 as being obvious over Hays, Hersch, Allen, Fujii and O'Rear.

(4) Rejection of claim 57 under 35 U.S.C. § 103(a) as being unpatentable over Hayes alone or in combination with Hersch, Allen, Fujii, O'Rear, individually or in combination as set forth above, further in view of Anaissie (US Patent No. 4,999,199, hereinafter "Anaissie")

Claim 57

Claim 57 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1.

Claim 57 is not obvious over Hays alone or in combination with Hersch, Fujii, or O'Rear for reasons similar to those discussed above. Hays does not discuss a liposome that comprises DOPC:Cholesterol, and does not discuss a formulation of DOPC:Cholesterol in a ratio of about 2:1. Fujii, O'Rear, and Hersch neither individually nor in combination with Hays remedy the deficiencies of Hays because none of these references teach or suggest all the features of the present claimed invention. Hersch does not teach or suggest a formulation of DOPC:Cholesterol. Allen used egg phosphatidylcholine (egg lecithin), DPPC or DSPC, none of which are recited by the present claims. Fujii used DSPC and cholesterol, which is not recited by

the present claims. O'Rear used POPC, which is not recited by the present claims. Thus, the presently claimed liposomes are different structurally and are functionally distinguishable over those discussed by Hays, Hersch, Allen, Fujii, and O'Rear.

Anaissie discusses the preparation of liposomes that are stable multilamellar vesicles that comprises phospholipids and may include a sterol such as cholesterol (col. 3, lines 48-64). In particular, Anaissie discusses the use of the lipids Egg phosphatidylcholine (EggPC), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), dielaidoylphosphatidylcholine (DEPC), phosphatidylthanolamine (PE), dioleolylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), dipalmitoylphosphatidylcholine (DPPC) and cholesterol (col. 7, lines 19-28). Anaissie, however, does not teach or suggest the formulation of DOPC:Cholesterol in a ratio of about 2:1, as recited by claim 57. Anaissie, only mentions the mixture of EggPC/cholesterol at a ratio of 9:1; the mixture of DMPC/DMPG at a ratio of 7:3; mixtures of DPPC/PE/cholesterol, DSPC/PE/cholesterol, or DEPC/PE/cholesterol in a ratio of 6.5:2.5:1; and the mixture of DOPC/PE/cholesterol in a ratio of 6:3:1.

Accordingly, the Hays, Hersch, Allen, Fujii, O'Rear and Anaissie references when taken singly or in combination do not teach or suggest the all of the features of the liposomes recited in the instant claims. Therefore, Applicant requests that the Board reverse the Examiner's rejection of claim 57 as being obvious over Hays, Hersch, Allen, Fujii, O'Rear and Anaissie.

CONCLUSION

As discussed above, a significant body of literature exists relating to the use of liposomes to deliver drugs. In spite of this, there was a need to find the correct combination of components that could be used to produce liposomal systems that would be useful for delivering lipophobic therapeutic agents to humans. Such liposomal systems did not exist. Applicant has identified and is currently claiming specific liposomal compositions that deliver lipophobic therapeutic agents with intermediate release half lives.

The Examiner has identified seven documents from the existing body of liposome art and has generally concluded that one skilled in the art could have found the claimed compositions by selecting components from, in some cases, combinations of five or six of the cited documents. It is submitted that the Examiner has looked back into the broad generic knowledge of the

liposomal delivery field and reconstructed the claimed liposomal compositions from small unrelated segments within the seven cited documents. There are no teachings or guideposts in the cited documents that would have suggested to one skilled in the art the selections necessary to arrive at the claimed invention. In fact, none of the cited documents include the component ratios that are specifically recited in the claims. These recited component ratios provide liposomes with useful intermediate release properties for lipophilic therapeutic agents.

Applicant respectfully submits that the Examiner has not met the burden required to establish that claims 54-58 are *prima* facie obvious over the cited documents. Accordingly, withdrawal of the outstanding rejections is appropriate and is respectfully requested.

In light of the remarks provided hereinabove, Applicant believes that the claims are in condition for allowance, and notification to that effect is respectfully requested. If necessary, please charge any additional fees or credit overpayment to Deposit Account 50-3503.

Respectfully submitted,

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Date: 22 July 2010

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(8) Claims Appendix.

54. A formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1.

55. A formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol in a ratio of about 2:1.

56. A formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1.

57. A formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1.

58. A formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1.

(9) Evidence Appendix.

1. Hersch (US Patent No. 5,759,571)
   This document was entered by the Examiner in the Office Action dated March 16, 2007.

2. Allen (*Biochimica et Biophysica Acta*, 597(1980): 418-426)
   This document was entered by the Examiner in the Office Action dated September 9, 2008.

3. Fujii (US Patent No. 5,328,678)
   This document was entered by the Examiner in the Office Action dated September 9, 2008.

4. O'Rear (US Patent No. 5,503,850)
   This document was entered by the Examiner in the Office Action dated September 9, 2008.

5. Lopez-Berestein (US Patent No. 5,032,404)
   This document was entered by the Examiner in the Office Action dated March 16, 2007.

6. Hays (US Patent No. 5,869,092)
   This document was entered by the Examiner in the Office Action dated September 9, 2008.

7. Anaissie (US Patent No. 4,999,199)
   This document was entered by the Examiner in the Office Action dated March 16, 2007.

(10) Related Proceedings Appendix.

None.